Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Dolutegravir (DTG, Tivicay) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Tablets: 10 mg, 25 mg, 50 mg

Fixed-Dose Combination Tablets:

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose:

- Dolutegravir (DTG) is not approved for use in neonates or infants.

Child (Weighing <20 kg) Dose:

- No dosing recommendations can be made for children weighing <20 kg.

Child and Adolescent (Weighing ≥20 kg to <40 kg) Dose:

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using an investigational dose of DTG 50 mg once daily for children and adolescents weighing ≥20 kg who are antiretroviral therapy (ART)-naive or ART-experienced (but integrase strand transfer inhibitor [INSTI]-naive) and who are not being treated with uridine diphosphate glucuronyl transferase (UGT) 1A1 or cytochrome P450 (CYP) 3A inducers or inhibitors.
- DTG is not approved by the Food and Drug Administration (FDA) for use in children weighing <30 kg. However, interim data from ongoing trials indicate that using the FDA-approved dose of DTG 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations, and additional data supports the 50-mg dose recommended by the Panel (see text). Using a 50-mg dose also avoids the need to administer two tablets with different strengths (i.e., a 10-mg tablet plus a 25-mg tablet).

Selected Adverse Events

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness
- Rare cases of hypersensitivity reactions, including rash and drug reaction (or rash) with eosinophilia and systemic symptoms, constitutional symptoms, and organ dysfunction (including liver injury) have been reported.

Special Instructions

- DTG may be taken without regard to meals.
- DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.
- In patients who have difficulty swallowing tablets whole, 10-mg, 25-mg, and 50-mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.[1]
- The efficacy of DTG 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

Population	Recommended Dose
ARV-naive or ARV-experienced/ INSTI-naive patients	DTG 50 mg once daily
ARV-naive or ARV-experienced/ INSTI-naive patients who are also receiving one of the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ ritonavir, or rifampin	DTG 50 mg twice daily[a]
INSTI-experienced patients with any INSTI-associated resistance mutations or clinically suspected INSTI resistance	DTG 50 mg twice daily[a,b]

[a] The 50-mg, twice-daily dose **should not be used** in patients weighing <40 kg.

[b] These patients should receive drug combinations that do not include metabolic inducers when possible.

[Dovato] Dolutegravir/Lamivudine

Adult Dose:

- One tablet once daily with or without food as a complete regimen in ARV-naive adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug (see the Simplification of Treatment section below).

[Juluca] Dolutegravir/Rilpivirine

Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.
- Juluca is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen (see the Simplification of Treatment section below.

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily with or without food.
- For use in patients who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not
- Patients should be tested for hepatitis B virus (HBV) infection prior to use of Triumeq or Dovato. Lamivudine (3TC)-resistant HBV variants have been reported in patients who received 3TC-containing ARV regimens. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection. Severe exacerbation of hepatitis can occur in patients with HBV/HIV coinfection who discontinue 3TC.

Metabolism/Elimination

- UGT1A1 and CYP3A substrate. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes may increase DTG plasma concentrations.

Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to a lack of data, DTG **is not recommended** for use in patients with severe hepatic impairment.
- DTG decreases tubular secretion of creatinine and increases measured serum creatinine, without affecting glomerular filtration.

Dolutegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.

being treated with UGT1A1 or CYP3A inducers.
- See the Abacavir section for special instructions about testing for abacavir hypersensitivity.
- The FDA-approved dose for pediatric patients weighing ≥40 kg is one tablet once daily.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A1 and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. Because etravirine (ETR) significantly reduces plasma concentrations of DTG, DTG **should not be administered** with ETR without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on DTG concentrations. DTG **should not be administered** with nevirapine because of insufficient data on interactions between these drugs.
- Atazanavir (ATV) is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving DTG, patients who also received ATV had plasma concentrations of DTG that were two-fold to four-fold higher than those of patients who received other antiretroviral (ARV) drugs.[2]
- Before administering DTG, clinicians should carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- *More common:* Insomnia and headache. Weight gain has been reported in adults who received DTG (see Table 15h–Lyodystophies and Weight Gain).
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction. Neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note that neuropsychiatric adverse effects (AEs) have occurred after initiation of DTG-based therapy in adults.[3,4]
- *Immune reconstitution inflammatory syndrome (IRIS)*: In retrospective observational studies, severe cases of IRIS that required hospitalization appeared to be more frequent in patients who presented with advanced disease and who initiated treatment with integrase strand transfer inhibitors (INSTIs), particularly DTG.[5,6] This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving INSTI-based therapy.
- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of DTG. One of these cases required liver transplantation.[7,8]
- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.[9]
- *Rare:* In a prospective surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana, a small but significant increase in the risk of neural tube defects (NTDs) has been observed among infants born to women who were receiving DTG at the time of conception.[10] Before patients become sexually active, pediatric and adolescent providers should discuss the potential risk of NTDs with patients who are receiving or initiating DTG and their caregivers so that they can make informed decisions about its use (see Appendix D. Dolutegravir Counseling Guide for Health Care

Providers in the Perinatal Guidelines). Specific recommendations about the initiation and use of DTG in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance database offers a discussion of each mutation.

The efficacy of DTG 50 mg twice daily is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

Pediatric Use

Approval

DTG is approved by the Food and Drug Administration (FDA) for use in combination with other ARV drugs in children and adolescents weighing ≥30 kg who are treatment-naive or treatment-experienced but INSTI-naive at DTG doses that are lower than the adult dose. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using the adult dose in children and adolescents weighing ≥20 kg (see Appendix A, Table 2).[11] The World Health Organization (WHO) also recommends using DTG at the adult dose of DTG 50 mg in children weighing ≥20 kg.[12] These recommendations are based on pharmacokinetic (PK) and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY) that are described below. The combination tablet abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Triumeq) is approved by the FDA for use in children and adolescents weighing ≥40 kg, although the Panel recommends using it in children and adolescents weighing ≥25 kg (see Appendix A, Table 2).[13] The combination tablets dolutegravir/rilpivirine (DTG/RPV; Juluca) and dolutegravir/lamivudine (DTG/3TC; Dovato) are not approved by the FDA for use in children or adolescents at the time of this review,[14,15] and the Panel **does not recommend** using these drugs.

Table A. Comparison of Food and Drug Administration, European Medicines Agency, World Health Organization, and Panel Dosing Recommendations for Dolutegravir Film-Coated Tablets

Body Weight	FDA-Recommended Dose[a]	EMA-Recommended Dose[a]	WHO-Recommended Dose[a]	Panel-Recommended Dose[a]
15 kg to <20 kg	NRS	20 mg[b]	NRS	NRS
20 kg to <30 kg	NRS	25 mg	50 mg[d]	50 mg[d]
30 kg to <40 kg	35 mg[c]	35 mg[c]	50 mg[d]	50 mg[d]
≥40 kg	50 mg	50 mg	50 mg	50 mg

[a] All doses are administered once daily.

[b] Administered as two 10-mg film-coated tablets.

[c] Administered as one 25-mg film-coated tablet and one 10-mg film-coated tablet.

[d] Weight categories have been altered to fit this table. Both WHO and the Panel recommend DTG 50 mg for children weighing 20 kg to <40 kg.

Key: DTG = dolutegravir; EMA = European Medicines Agency; FDA = Food and Drug Administration; NRS = no recommendation specified; Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; WHO = World Health Organization

Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet

DTG is currently available as a film-coated tablet. A dispersible tablet has been developed and is being studied for use in those who cannot swallow tablets. The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,[16] so doses studied using the dispersible tablet cannot be

directly compared to those using the film-coated tablet. The drug exposure of the 50-mg film-coated tablet is approximately equal to the drug exposure of DTG 30 mg administered as dispersible tablets. A previously investigated DTG granule formulation is no longer being studied.[17]

Efficacy and Pharmacokinetics

Children and Adolescents Aged ≥12 Years and Weighing ≥40 kg

IMPAACT P1093 is an ongoing, open-label trial of DTG in children with HIV. Initial FDA approval of DTG for use in adolescents weighing ≥40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.[18] Intensive PK evaluations were performed on the first 10 participants, nine of whom weighed ≥40 kg and received DTG 50 mg and one of whom weighed 37 kg and received DTG 35 mg. These doses resulted in exposures that were comparable to those seen in adults who received DTG 50 mg once daily. Nine of 10 participants achieved HIV RNA levels <400 copies/mL at Week 4 (optimal background therapy was added 5–10 days after DTG was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% of participants had achieved HIV RNA levels <50 copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA levels <400 copies/mL and <50 copies/mL, respectively. All participants who experienced virologic failure were nonadherent.

Additional long-term safety and efficacy data for this age/weight group comes from a retrospective, multicenter French cohort study that evaluated 50 adolescents who initiated DTG-based ART. Of 17 adolescents who were virologically suppressed at the time of DTG-based treatment, 14 (82%) maintained suppression and three had transient viral rebound prior to re-achieving a plasma viral load <50 copies/mL. Of the 33 viremic adolescents who initiated DTG, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression and 78% had undetectable plasma viral loads by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and were more likely to have detectable viremia in the 6 months prior to DTG initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued DTG-based treatment because of a significant AE (dizziness and sleep disturbance).[19]

Another cohort of adolescents in Barcelona received the fixed-dose combination (FDC) product ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the twelve patients described, one received Triumeq for initial ART, six received Triumeq for treatment simplification, and five received Triumeq because of previous treatment failure. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients failed to achieve suppression due to suboptimal adherence. Of note, patients complained about the size of the tablet, and six patients reported having to crush or split the tablet in order to swallow it (see Appendix A, Table 2).[20]

Children and Adolescents Aged <12 Years

A younger cohort of children aged ≥6 years to <12 years underwent PK assessment and remains in long-term follow up in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving DTG 35 mg and those weighing ≥40 kg receiving DTG 50 mg. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PKs, and virologic efficacy, with HIV RNA levels of <50 copies/mL achieved in 17 of 23 participants (74%).[18,21] These data led to FDA approval of the lower-strength, film-coated DTG tablets at a dose of 35 mg for use in children with HIV who weigh ≥30 kg to <40 kg. The FDA did not approve a DTG dose for use in children weighing <30 kg because the PK data in the lower weight bands were limited and the observed C_{trough} concentrations in patients in these weight bands were lower than expected.

The ODYSSEY trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA) is enrolling both treatment-naive and treatment-experienced pediatric patients in the European Union (EU), Thailand, and several African countries; this trial initially evaluated doses that were approved by the European Medicines Agency (EMA; see Table A above). A total of 674 children aged <18 years were enrolled; 282 children started DTG as first-line therapy and 392 started DTG as second-line therapy.[22] Nested PK substudies within ODYSSEY are also evaluating simplified pediatric dosing that aligns with WHO-

recommended weight bands. PK data are available from a cohort of children weighing >25 kg who switched to the 50-mg DTG tablet (n = 27). Children weighing ≥25 kg who received the 50-mg, film-coated DTG tablet achieved exposures similar to those seen in adults who received the same dose. When given to children weighing 14 kg to <25 kg, the 25-mg, film-coated DTG tablet resulted in drug exposures that were lower than the target exposure for adults, particularly C_{trough}. The median C_{trough} was lower in the 20 kg to <25 kg group than in the 14 kg to <20 kg group.[23,24] Data from ODYSSEY was recently reported on children weighing 20 kg to <25 kg who received either the 50-mg film-coated tablet or 30 mg of DTG administered as six 5-mg dispersible tablets. Both of these doses achieved area under the curve (AUC) and C_{max} values that were higher than adult PK reference values, but still acceptable, and both doses achieved C_{trough} values that were similar to adult reference values.[25] At this time, neither the FDA nor the EMA have reviewed the data supporting the use of the 50-mg film-coated tablet in children weighing between 20 kg and <40 kg.

The EMA used the IMPAACT P1093 data to inform population PK modelling and simulation analyses to approve the lower-strength, film-coated DTG tablets for use in children aged ≥6 years and weighing ≥15 kg.[26] The EMA approved doses of DTG 20 mg for children weighing 15 kg to <20 kg and doses of DTG 25 mg for those weighing 20 kg to <30 kg (see Table A above). As noted, evaluation of these doses during the ODYSSEY study indicated that many children failed to achieve adequate trough concentrations. The Panel **does not recommend** the use of DTG in children weighing <20 kg until further data are available to determine an appropriate dose for this weight group.

The safety and effectiveness of the EMA dosing strategy was evaluated in a cohort of children aged 6 years to <18 years in the United Kingdom and Ireland who were followed during the CHIPS study. Between January 2014 and March 2018, 174 children in the cohort received DTG at the EU-licensed doses (see Table A above). Of these 174 children, 53% were female and 91% had perinatally acquired HIV, and the median age was 15.5 years at DTG initiation (interquartile range 13.5–16.7 years). Only 6% of the cohort was treatment-naive, and 38% had previous exposure to three classes of ARV drugs. Overall, nine participants (5%) discontinued DTG; three discontinued because of toxicity, three discontinued because an alternative regimen was available, and three discontinued for other or unknown reasons. Viral suppression was reported in 80 of 95 participants (84%) who remained on DTG for 6 months, and viral suppression was reported in 41 of 49 participants (84%) who remained on DTG for 12 months. Median changes in CD4 T lymphocyte cell counts were -9 cells/mm^3 at 6 months (n = 81) and +47 cells/mm^3 at 12 months (n = 41) of DTG treatment.[27]

Children Aged <6 Years Who Are Not Able to Swallow Tablets: Dolutegravir Dispersible Tablets

The first presentation of the data on DTG dispersible tablets reported that three age cohorts of 10 patients (≥4 weeks to <6 months, ≥6 months to <2 years, and ≥2 years to <6 years) received protocol-defined, weight-based dosing using combinations of 5-mg dispersible tablets. While target AUC_{24h} and C_{24h} levels were achieved in the youngest cohort, C_{24h} levels were low in children aged 6 months to <6 years. The dispersible tablet formulation was well-tolerated by all age groups. Higher doses are being evaluated in some age/weight groups.[28]

Simplification of Treatment

Two trials in adults (SWORD-1 and SWORD-2) supported the approval of a DTG 50 mg/RPV 25 mg FDC tablet (Juluca) as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 virologically suppressed patients who had been on stable ART for at least 6 months and who had no history of treatment failure or evidence of resistance mutations. The participants were randomized to either receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA levels <50 copies/mL.[29] More AEs were reported and led to discontinuation in the DTG/RPV arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate (TDF), small but statistically significant increases in hip and spine bone mineral density were observed.[30]

The approval of DTG 50 mg/3TC 300 mg (Dovato) as a complete regimen was supported by data from two randomized, double-blind, controlled trials (GEMINI-1 and GEMINI-2) in ARV-naive adults with HIV. GEMINI-1 and GEMINI-2 are identical, 148-week trials that enrolled a total of 1,433 adults with HIV who had

plasma HIV RNA levels between 1,000 copies/mL and ≤500,000 copies/mL at screening and no evidence of major resistance mutations or hepatitis B virus infection. Participants were randomized to receive either DTG plus 3TC or DTG plus 3TC/TDF. During 48 weeks of treatment, 91% of patients who received DTG plus 3TC and 93% of patients who received DTG plus 3TC/TDF achieved HIV RNA levels <50 copies/mL. Similar proportions of patients discontinued treatment due to AEs or other reasons in the two treatment arms.[31]

Although neither Juluca nor Dovato is approved by the FDA for use in adolescents, the doses of the component drugs that make up these FDC tablets are approved for use in adolescents. The Panel usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulty adhering to therapy, the Panel **does not currently recommend** using two-drug simplification regimens in adolescents and children until more data are available.

Crushing Film-Coated Tablets for Administration

In patients who have difficulty swallowing whole tablets, the 10-mg, 25-mg, and 50-mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.[1] Crushing and mixing film-coated tablets would not be expected to adversely impact the product's pharmaceutical quality, and therefore would not be expected to alter the intended clinical effect. This conclusion is based on the physicochemical and PK characteristics of the active ingredient, and the *in vitro* dissolution behavior of the film-coated tablets in water. In healthy adults, the use of crushed tablets resulted in slightly higher exposures than the use of whole tablets.[32]

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